to my assistance, to do the most important part of the work, Dr. James Carroll. It would be impossible for me to offer any results of our work, so far made, without doing violence to their future value; therefore I am not able to go to any extent whatever as to our present findings. I add, as a present addition to this subject, a most excellent photomicrograph of one of our sections, which on study shows, without doubt, that however the change is brought about, the resulting pathological lesion is a keratosis.

These sections are all alike, except that some show the changes a little more perfectly than the others. This being one of the clearest specimens, I send it as an accompaniment to my paper.

On the surface of the mucosa will be seen the frequent piling up of the stratified epithelial cells, which evidently made up the tuft, which was broken at the apex by the pressure of the knife. Just below the stratified epithelial layer will be seen the thickened normal epithelial layer, and beneath that the tonsillar structure.

The photomicrograph demonstrates in a most perfect manner the actual keratoid changes which have taken place.

A PRELIMINARY STUDY OF THE OCULAR CHANGES PRODUCED BY THE INJECTION OF PURE CULTURES OF THE BACILLUS TYPHOSUS INTO THE VITREOUS CHAMBERS OF RABBITS AND GUINEA-PIGS.[1]

By Charles A. Oliver, A.M., M.D.,
of Philadelphia.

The results herein noted constitute but a portion of those that have been obtained by the writer during a series of experiments which have continued through a period of nearly three years' time.[1] In order to render the reading of the paper brief, logical, and intelligible, many details that are of value not only to the ophthalmologist, but also to the physiologist, the neurologist, and the general practitioner, have been omitted from the text of the report and relegated to foot-notes.

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[1] Read at the meeting of the American Ophthalmological Society, July, 1902.

Experimental work upon injections of chloride of sodium into the anterior chamber and into Tenon's space is now being tried in order to study the histological findings of any abortive effects that they may have upon the minor forms of bacteria invasion and inflammatory reaction.

General studies, both clinical and histological, to show the effects of vitreal colonization cultures upon other animals of similar kind and equal bulk are being prepared.

A series of experiments in an endeavor to show the routes of interocular lymph circulation are being made in a number of novel but strictly scientific ways. As early as is compatible for certainty of results the findings will be reported.

Culture studies from the mesenteric glands, the spleen, the liver, the bile, the bone marrow, and particularly the lymph channels of the cerebro-spinal system and its peripheral sense organs, will be made upon the visual structures.

Attempts at vitreous inoculation will be made upon animals which have been immunized as fully as possible in order to study the earliest and most minute evidences of local effects and thus to compare mere aseptic traumatic leucocytoses with pyogenic infections.

Instillations and injections of weak solutions of definite strengths of formalin, which drug is said to be a most excellent agent for killing the bacilli without disturbing the diagnostic qualities or the agglutinating signs, will be made upon induced mild cases of typhoid fever in the rabbit to determine whether the drug can be made of therapeutic value.

The type[2] of the bacillus employed was proved by the non-coagulation of milk with the ordinary tests; the inability to give rise to sugar fermentation with lactose agar; the absence of indol with and without the use of nitrites; and the production of alkaline reaction, or at least minimal degree of acidity, when associated with litmus milk before the micro-organism was used for injection purposes. To be doubly certain, the reactions to the blood serum of an immune animal and the agglutination tests were obtained.[3]

Pure cultures of the bacillus were injected aseptically into the upper outer anterior portion of the vitreous chamber of the animals, through a puncture made in the scleral coat, back of the ciliary region, mid-way between the insertions of the external and the superior rectus muscles.

The germ was inserted directly into the eyeball—ectogenously, as it were—a true primary bacillar infection, without any intermediate steps. The micro-organism was placed in a lymph organ which is in direct, close, and independent communication with the intracranial fluids.

The clinical expressions were rapid in their appearance. As a part of the general symptoms there were varying degrees of hyperpyrexia, lasting twelve to sixteen days. The animals soon refused food and lost weight, although carefully cared for. A number of them, particularly the rabbits, developed the characteristic signs of a true myelitis: some succumbed to toxin asthenia.

Locally, the iris became involved in from twenty to forty hours' time.

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[1] Some of the primary work in these researches was done in the Pathological Laboratory of the Philadelphia Hospital, some in the Pathological Laboratories of the Department of Medicine of the University of Pennsylvania, and some at Wills Hospital. Many of the later experiments were performed in the private laboratory of the writer and at the home of one of his former assistants and friends, Dr. Van Scholck, of Hightstown, N. J.

In all, fifty-four healthy animals were studied; some twenty privately, twenty-four at the University of Pennsylvania, and the remaining number at the Philadelphia Hospital: of these, forty-six were rabbits.

The writer is under obligation to Dr. Simon Flexner, Napoleon B. Boston, Richard M. Pearce, and William F. Hendrickson for many suggestions throughout the studies. To Dr. I. L. Van Scholck and Clarence Van Epps he is grateful for assistance during the experiments. He is indebted to Dr. John T. Krall for most conscientious research work. He also desires to express his gratitude to Miss Mary C. Koonce, Miss Paula B. Himmelsbach, and Miss E. C. Potter for the execution of the many water-color sketches that have been rendered necessary in the proper pursuance of the work.

[2] For all of the primary experiments the human bacillus carefully obtained in pure cultures, and in some instances grown through several generations and proven to be still virile and able to reproduce the general disease, was used; rabbit cultures were employed in some of the later experiments.

[3] The cultures of these injection materials were kept *pari passu* with the series made from the intra-ocular fluids that had been aspirated at varying periods of time.

The primary manifestations consisted in a thickening of the stroma, the appearance of numerous radially arranged vessels, and the development of a number of clump-like hemorrhages at the major and minor circles. Scattered throughout the posterior chamber, and in the pupillary area, free erythrocytes mingled with fibrin and polymorphonuclear leucocytes could be seen. The retinal pigment layer of the iris was but little disturbed. The bloodvessels of the chorioid evidenced considerable injection, and in some situations the tissues of the membrane were œdematous. At this period a few deeply seated chorioidal and probably retinal hemorrhages, with fibrillary bands and dust-like opacities in the vitreous humor could be recognized.[1] The cornea was infiltrated in its deeper layers, and new blood channels sprang from the limbal series, penetrating the membrane in all manner of fantastic ways, but more often ranging in straight radial lines. In this stage, Descemet's membrane was found to be intact.

In a more pronounced stage, or as a separate condition, the conjunctival membrane and the subconjunctival tissues, especially around the corneoscleral junction, became œdematous and swollen, until in many instances the cornea was set in a deep and sharply circumscribed pit. The palpebral conjunctiva was but slightly affected, and the eyelids apparently did not participate actively in the process. The tissues around the point of inoculation were never more involved than were the other areas of inflammatory reaction. In many instances the vitreous chamber was in great part occupied by broad, yellowish masses, which reached almost as far forward as the posterior capsule of the lens. A number of these cases showed a beginning increase in intraocular tension. Early in this stage the retina evidenced such extensive infiltration with leucocytes of polymorphonuclear type, that all appearance of retinal structures often was obliterated. Considerable extravasation of red blood cells into the tissues could be determined in some situations.[2] There were many accumulations of inflammatory exudate, serum, leucocytes, and erythrocytes.

Grosser forms exhibited an increase of all of the previous conditions, with a number of superadded signs of coarse, degenerative type. Portions of the corneal epithelium were denuded, the underlying lamellæ exhibiting minute areas of necrosis. The iris showed numerous thickenings, discolorations, and, rather infrequently, a few fine plastic lesions. The lens[3] and the capsules were opaque and tumescent in places. The external structures were much swollen and catarrhal. There was a true lessening of intra-ocular tension.

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[1] No qualitative blood studies have been established as yet.

[2] In some places the amount of exudate of serum and corpuscular elements was so marked that the retina was found to be separated from the chorioid, giving an appearance resembling ordinary blisters.

[3] The crystalline lenses have been set aside for special study, though the presence of the bacillus in these structures has been proved by pure growths obtained in culture colonization.

The last stages exhibited numerous atrophic signs. In many of the first cases studied, the eyeball had shrunk into a small, irregular, and hardened stump, fixed in a mass of coarse, fibrinous tissue. Over this crossed the remnants of a cicatrized and band-like conjunctiva, dragging the thinned and irregularly shaped lids against itself.

At varying periods during the many stages of these reactions, minute quantities of the infected vitreous humor were carefully aspirated and placed in various culture media. Most of these withdrawals were made through the corresponding inner sides of the anterior segments of the eyeballs.[1]

Cover-slip preparations of the withdrawn vitreous fluids showed motile typhoid bacilli, with peritrichially arranged flagella, these bacteria exhibiting their peculiar properties of not being able to retain aniline dyes when treated by the Gram or Weigert methods.[2]

In many, if not in all of the cases, the infected portions of the withdrawn vitreous humor were found to be translucent where filled with bacilli. Nearly all of the specimens of removed aqueous humor were more or less albuminous in character.

After preparation of the tissues in different ways several hundred sections showing the combined effects of the germ and the traumatism upon all of the ocular tissues were obtained. These specimens were studied in every detail.[3] The main characteristics were as follows: In sections of the early stage, portions of the ciliary bodies and adjacent uveal structures—probably the glandular tissues—were swollen, and in some instances were found to contain aggregations of typhoid bacilli. Penetrating and surrounding these tumescent parts were numerous dilated capillaries and newly formed bloodvessels, from which the typhoid bacillus could be isolated in a number of instances. In direct connection with the lymph organs there were numbers of large, free masses of the bacilli. Further back, the superficial layers of the retina were found to be richly infiltrated with polymorphonuclear cells and leucocytes. As early as the fourth day free hemorrhages were found irregularly distributed throughout the fibre layer and deeper portions of the retina, particularly in the circummacular regions, just below the outer extension of the normally retained nerve sheaths of the animal.[1] Rather deeply placed and more forwardly situated hemorrhagic extravasations from the two inner vascular layers of the chorioid were found in two or three of the cases.

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[1] The rule that was made was that, although different amounts of the material were injected, yet the most minute quantity possible was withdrawn.

[2] Attempts for agglutination processes within the ocular bulb (which is particularly rich in lymph glands), showing the effects of development, growth, and colonization modifications upon the already inflamed contiguous structures will be tried, not for diagnostic purposes, but for actual therapeutic gain. For this purpose variable strengths of dilute serum will be employed. Widal's reaction studies will be applied to this particular phase of the work.

[3] These studies have nothing whatever to do with the many post-febrile conditions which are so constantly quoted as being associated with and following typhoid fever, and which at best are merely concomitants and sequelæ of any form of continued hyperpyrexia. Such conditions cannot be considered as pathognomonic of the disease.

There were not any coarse indications of pyogenic infection in this grade of sections.

In the grosser stages, many of the sections showed an acute endarteritis in association with the bacilli.[2] Some of the specimens exhibited changes that indicated toxin action; others[3] evidenced signs of well-marked secondary infection. In the majority of the non-lethal cases sanguineous extravasations with some erythrocytic aggregations and leucocytic masses were seen. At times, hyperplasia and even degenerative changes in the adjacent tissues were manifest. In some of the cases, both arteritis and periarteritis and phlebitis and periphlebitis could be seen near the larger lymph cavities and main lymph channels.

In the coarser groupings, there were all the marks of erosion of the walls of the larger vessels, with gross signs of pyogenic invasion throughout the now greatly disorganized tissues. In the equatorial sections especially, secondary phlebitis with streptococcal and staphylococcal invasion of the clots and venous coats—true sepsis—could be determined. Many thrombi composed of fibrin-laden leucocytes, situated mostly in the lymphatic channels and main venous stems, could be seen, the containing walls in places being excessively attenuated. In the more marked cases there were localized abscesses. Pyogenic micro-organisms were obtainable in excessive amounts in nearly all of the ocular tissues.

The last stages showed all manner of connective-tissue growth. Well-pronounced foci of cell death—leucocytic in part—surrounded areas of necrotic tissue, which at times were almost indeterminable. The bacillus typhosus was now most difficult to find, only an occasional stray one being seen.[4]

[1] Rabbits.

[2] This finding substantiates Keen's belief in microbic invasion as the cause of retinal hemorrhage.

[3] Not many signs in this stage of the condition.

[4] True optic neuritis was often present in cases in which the eyeball was destroyed, but in most instances it was of pronounced type, and it never involved the fellow organ. Several times a very low grade of the condition, as secondary to uveitis, was seen ophthalmoscopically. In this connection it must be remembered that the primary invasion of the germ was through the eye.

The presence of the germ in the meninges and the linings of the lymph channels of the brain was more than once noted during the cursory examinations vouchsafed these structures by the writer.

In the vast majority of cases, oculomotor changes in typhoid fever are dependent upon intracranial disturbance, but it is conceivable, nay, probable, that a true peripheral neuritis from the actual presence of the bacillus typhosus and its frequent associates, particularly in the vascular and lymph channels of the muscular and other tissues of the orbit, can give rise to

Bacteriological examination of the inflamed conjunctivæ showed true secondary infection; pneumococci, staphylococci, and streptococci being present in the tissues, fluids, and secretions. Orbital involvement was not infrequent.

In one of the cases which had progressed from a slow form of suppurative panophthalmitis to a phthisical globe, the bacillus typhosus was found nested in the extra-ocular orbital contents in several situations, substantiating Swanzy's belief concerning the same and proving Panas' findings.[1]

In a word, every portion of the organ is affected.[2] The ocular expressions of the presence of the germ are protean and panophthalmic; the low-grade uveites, keratites, and retinites being principally primary, and the ophthalmites, gross conjunctivites, and orbital cellulites mainly secondary.[3]

Remarks. Presupposing that the tissues or "soils," as they are called, were as near alike as possible, the symptoms varied with the dosage.[4] The majority of the eyes perished with the amounts of injections at first used. Later, with the employment of lesser amounts and the same technique, most of the eyeballs, though ofttimes functionless, were saved. In a few, the symptoms subsided early, and the eyes were able to functionate.[5]

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localized peripheral palsies and trophic changes. Of course, true extension of pyogenic inflammation along the nerve, vessel, and lymph channel tracts may take place from contiguous areas of primary bacillar inflammation, and as a result no bacilli be found in the extra-ocular structures.

[1] Since the time that the main experiments were made several cases studied by the writer showed that the other eye could be made to participate in the characteristic manner of typhoid inflammation by an injection of a slight amount of streptococcal matter into it, true typhoid germ colonization areas being found in the interior of the organ, thus proving in a measure the earlier finding, that a few stray bacilli from endogenous infection may produce fine retinal and chorioidal hemorrhages in the constitutionally affected organ.

[2] Traumatic infection during the experimental procedures, in the minor cases at least, can be set aside to some extent by the presence of the germinating bacillar colonies in the vitreous humor, the absence of pyogenic germs, and the distinct localization of the leucocytoses around the typhoid organism aggregations.

[3] In these two varieties there is merely an induced ocular type of the general disease. The fever may be induced by the primary entrance of the bacillus typhosus into the structure of the eyeball, not only giving rise to local effects, but also to general disturbances. This is particularly true in cases in which there is an already existent streptococcal invasion of the ocular bulb or surrounding lymph channels. It will thus be seen that it is possible to have a localized typhoid bacillus disease of the eye without general involvement. Introduced directly into an eyeball, either accidentally or intentionally, the micro-organism may germinate locally only and excite leucocytosis and bactericidal action of the serum and the blood to a sufficient degree to produce a primary infectious condition before being destroyed or rendered innocuous. Particularly is this so in cases in which lymph and consanguineous circulations are impeded, as, for example, in glycosuria and glaucoma.

[4] The bacillus typhosus belongs to what is known as the facultative anaërobic type—that is, it is a form of life which, while growing the best with a plentiful supply of oxygen, is able to exist with but a very small amount and even none at all.

[5] The well-known fact that typhoid fever bacilli can be carried within the human body for many years makes it entirely within the province of certainty that the germs may remain dormant, or even isolatedly colonizing very slowly and indefinitely in successive generations,

Experimentation showed that the bulk of the early intra-ocular conditions arose from the processes set into action by the actual presence of the typhoid bacilli themselves, and that they were not dependent upon a minor aseptic traumatism.[1] Vessel-wall erosion with hemorrhagic extravasation, lymph-gland infiltration with lymph- and blood-stream blockage, and increased leucocytosis with an abundance of the germ element were soon followed by the formation of bacillar colonization areas, giving rise to a punctate haze, with fibrillar opacities in the vitreous humor,[2] succeeded in turn by inflammation of the bacilli-laden coats of the ocular vessels. Thrombi appeared and leucocytosis became profound.[3]

The second stage—one of localized septicæmia in which suppurative processes, not only from the typhoid germs themselves, but also most probably from ectogenous inoculation through ruptured channels, ensued—pyogenic micro-organisms became prevalent and most virulent. At this period the bacillus typhosus began to disappear.

Later, the tissues degenerated; perforation through the ocular coverings, both from within and without, took place; the eyeball atrophied, and cicatrization bands of connective tissue, tying the organ into a motionless nodule, formed.[4]

Should the ocular conditions be less pronounced, and the lymph channels to the brain remain pervious and active, intracranial and spinal infections from the passage of the germ and its associates will early ensue, giving rise to all manner of coarse clinical signs of central disease.[5]

The minor degrees of endogenous type—in which there are slight and at times undisturbing and unsuspected retinal and uveal symptoms, as so frequently seen in the primary intestinal forms of the disease—are interesting, and prove what has been claimed ophthalmoscopically by a few competent clinicians.[6]

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within the eyeball for long periods of time. In such situations they may remain harmless until discharged into seral circulation by some traumatism or secondary degeneration of the surrounding tissue. For aught the writer knows the bacillus may yet be present (seven months at present writing) in the shrunken eyeballs of two rabbits which are being kept alive for other purposes.

[1] Coarse pathological examination cannot explain the etiology of the condition. Careful histological and bacteriological research, as in these studies, must always be instituted. The best results are obtained in cases in which there has been but a moderate degree of reaction

[2] Both Bull and Hansell describe this condition clinically.

[3] About this time general leucocytosis is most marked.

[4] In cases in which the animal had recovered from the gross local and general clinical signs of the primary vitreous infection, the second eye, when experimented upon, did not behave so badly as its fellow, this probably being due to the presence of germicidal serum in the vascular channels, or possibly even in the serum of the tissues of the animal.

[5] This may not be an infrequent cause for lethal result. The effects of the bacillus upon the intracranial prolongations of the visual apparatus will be considered in another communication. Nissl's method will be employed in a part of this work.

[6] It is possible that some of the cases of suppurative ophthalmitis occurring during attacks of typhoid fever, or even when individuals are exposed to infection from others, have arisen

The external ocular signs, which have been not infrequently described as associated with the general disease, can all be placed under the same categories of cause and effect, and are mere expressions of the main conditions.

The position in regard to the pathology that may be taken is that when the bacilli-laden serum gets into the interior of the eyeball, agglutinative processes followed by bacteriolytic changes which remove the bacilli take place. This destruction frees the toxins, which are either carried away or neutralized by the antitoxins. During these changes the invaded structures of the eyeball lose a few or many of their component parts, with the final result of either a useful organ, a functionless one, or a mere mass of degenerate tissue.[1]

PERFORATED GASTRIC ULCER; PERITONITIS; DEATH; DIAGNOSIS AT AUTOPSY.

By Astley Paston Cooper Ashhurst, M.D.,
RESIDENT PHYSICIAN AT THE EPISCOPAL HOSPITAL.

For permission to report the following case I am indebted to my chief, Dr. D. J. Milton Miller, in whose service at the Episcopal Hospital it occurred:

Kate J., single, white, aged fifty-seven years, occupation governess and companion, applied on January 29, 1902, for admission to the Episcopal Hospital, complaining of general malaise and a cold on the chest. She had been much interested in the work of the hospital about

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from the actual entrance of the bacterium into the eyeball itself through a break in the ocular tissue—a true ectogenous infection. It is probable, as hinted in another place in this communication, that the auto-infectious cases suffer the less—that is, if the general condition is relatively good.

[1] It is highly probable that the soluble toxins of the streptococcus diminish the protective leucocytosis of the organ. If not early destroyed by the bactericidal power of the serum and blood, they will permit a rapid growth with increased virulence of the typhoid germs, producing not only suppurative death of the organ, but also pronounced involvement of the cerebro-spinal cavities. Fortunately, in most cases of general typhoid invasion the streptococcal elements, unless locally introduced, are so frequent in the ocular bulbs that gross localized affections of the eyeball from the actual offensive presence of the typhoid germ are seldom seen.

It is probable that most of the reported instances of destructive eye changes in cases of typhoid fever have had previous or coetaneous breakages of the ocular walls, with the entrance of streptococcal material, the toxins of which have aided the bacilli to act much more decidedly, and thus give rise to expressions which could be recognized by coarse clinical study; conditions which perhaps have been simply superadded to existing signs of the disease, such as retinal and uveal hemorrhages.

In the intestinal type of the disease the micro-organism probably germinates in the lymphatic glands and then enters the lymph and blood circulation. In these researches the serum is thrown directly into one of the nearest, one of the most direct, and one of the largest lymph streams passing into those within the intracranial structures; thus probably giving rise to a more rapid and a more pronounced symptomatology of the nervous system than could be found in any other variety of ectogenous infection.